SYNTHESIS OF PIMPRININE AND RELATED OXAZOLYLINDOLE ALKALOIDS FROM N-ACYL DERIVATIVES OF TRYPTAMINE AND TRYPTOPHAN METHYL ESTER BY DDQ OXIDATION

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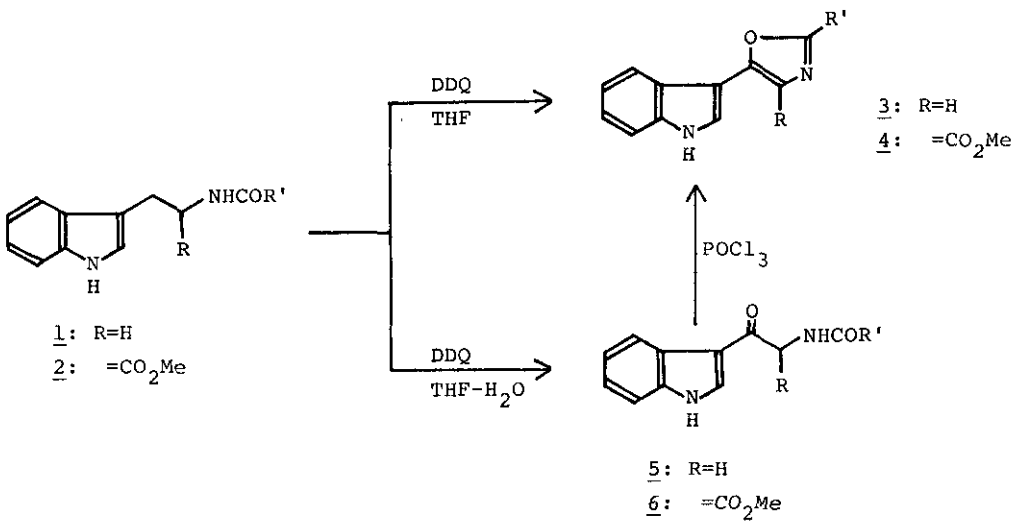
Abstract ——— N-Acyl derivatives of tryptamine and L-tryptophan methyl ester were treated with DDQ under anhydrous conditions directly to give pimprinine and related oxazolylindole alkaloids. Under aqueous conditions, the N-acyl derivatives were readily oxidized to the corresponding β-keto compounds, which were also converted to the oxazolylindoles by the treatment with $POCl_3$.

Pimprinine (3b), an alkaloid having antiepleptic[1] and monoamine oxidase inhibitory activities,[2] was first isolated from Streptomyces pimprina[3] and synthesized by Joshi et al[4] through the dehydrative cyclization of 1-acetyl-3-acetamidoacetylindole, though somewhat difficult to synthesize the starting material, 3-aminoacetylindole. Recently, Koyama et al isolated two very close alkaloids, pimprinethine (3c) and pimprinaphine (3h), as well as pimprinine (3b) from Streptoverticillium olivoreticuli and synthesized all the three compounds by an improved method via 3-(5-oxazolyl)indole (3a).[5]

We recently reported that 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) is the only reagent for the selective oxidation of side chains at C-3 of indoles.[6] Almost at the same time, the biological oxidation of this type was interestingly found, that is, Hayaishi et al isolated a new enzyme, tryptophan side chain oxidase from Pseudomonas, which oxidizes tryptophan derivatives to their β-hydroxy, β-keto, and α,β-dehydro compounds.[7] In the present paper, we wish to report an application of the DDQ oxidation for a biomimetic synthesis of pimprinine and a series of related compounds.[8]



1: R=H
2: =CO_2Me

3: R=H
4: =CO_2Me

5: R=H
6: =CO_2Me

a: R'=H
b: =Me
c: =Et
d: R'=i-Pr
e: =C_6H_5
f: =C_6H_4OMe(p)
g: R'=$C_6H_4NO_2$(p)
h: =$CH_2C_6H_5$
i: =$OCH_2C_6H_5$

When N-acetyltryptamine (1b) and DDQ (2 equiv) in THF was refluxed under argon for 50 min, pimprinine (3b) was formed directly and isolated quite easily, though in a very poor yield (10%), after passing through a short alumina column. The N-benzoyl compound (1e) similarly gave the corresponding oxazolylindole derivative (3e), but the yield was still unsatisfactory. Better results were obtained in the oxidation of N-acyl derivatives of tryptophan methyl ester (2), especially 2f having an electron-donative methoxybenzoyl group gave 4f in fairly good yield, whereas the nitro derivative (2g) gave again a poor result (Table I).

Table I. Oxazolylindoles (3, 4) from N-Acyl Derivatives of Tryptamine (1) and Tryptophan Methyl Ester (2) by DDQ Oxidation in Anhydrous THF.

1, 2		3		4	
	R'	Yield(%)	mp°C	Yield(%)	mp°C
b	CH_3	10	201-202	36	239-240
d	$CH(CH_3)_2$			55	194-195
e	C_6H_5	39	224-226	73	266-267
f	p-$CH_3OC_6H_4$			79	245-246
g	p-$NO_2C_6H_4$			22	296-298

When N-acyl tryptamines (1) were treated with DDQ (2 equiv) in THF-H_2O (9:1) under argon at room temperature for 1-2 hr, the corresponding β-keto products (5) were readily isolated in good yields regardless of the N-acyl group after passing through a short alumina column in EtOAc.[9] Similarly, N-acyltryptophan methyl esters (2), except 2e and 2f, were converted to 6 (Table II) with the concomitant formation of slight amounts of oxazolylindoles (4) having strong fluorescences, though only detected by tlc and uv spectra. Interestingly, 2e and 2f gave only the corresponding oxazolylindoles (4e, 4f), not β-keto derivatives (6e, 6f), even in the aqueous solvents.[11] No trace of 4g, on the contrary, was detected in the oxidation of 2g having an electron-withdrawing nitrophenyl substituent.

Table II. β-Keto Derivatives (5, 6) from 1 and 2 by DDQ Oxidation in THF-H_2O (9:1).

1, 2		5		6	
	R'	Yield(%)	mp°C	Yield(%)	mp°C
a	H	86	194-195	69	214(dec)
b	CH_3	73	216-218	84	202-205
c	CH_2CH_3	89	218-220	79	145-146
d	$CH(CH_3)_2$	78	212-213	74	157-159
e	C_6H_5	quant	213-214	72[a]	266-267
f	p-$CH_3OC_6H_4$	85	207-208	75[a]	245-246
g	p-$NO_2C_6H_4$	84	239-241	43	oil
h	$CH_2C_6H_5$	quant	215-217	80	150-152
i	$OCH_2C_6H_5$	86	230-232	71	oil

[a] Yield of 4, not 6.

Since 3-acylamidoacetylindoles (5) are known to give oxazolylindoles (3) by the dehydrative cyclization with $POCl_3$,[4,5] 5b-f,h were subjected to this reaction and the results are shown in Table III. This indirect synthesis from 1 is obviously superior at least in yield to the direct synthesis by the oxidation under anhydrous conditions. Practically, 3 were synthesized from 1 as follows: 1 and DDQ (2 equiv) in THF-H_2O (9:1) under argon were allowed to stand at room temperature for 1-2 hr. After evaporation of the THF, the residues were treated with 0.1 N NaOH to recover 2,3-dichloro-5,6-dicyanohydroquinone (DDHQ) and the precipitated solids were collected by filtration and washed with H_2O and EtOAc (decolorization). The dried solids (5) were refluxed in $POCl_3$ under argon to give 3.

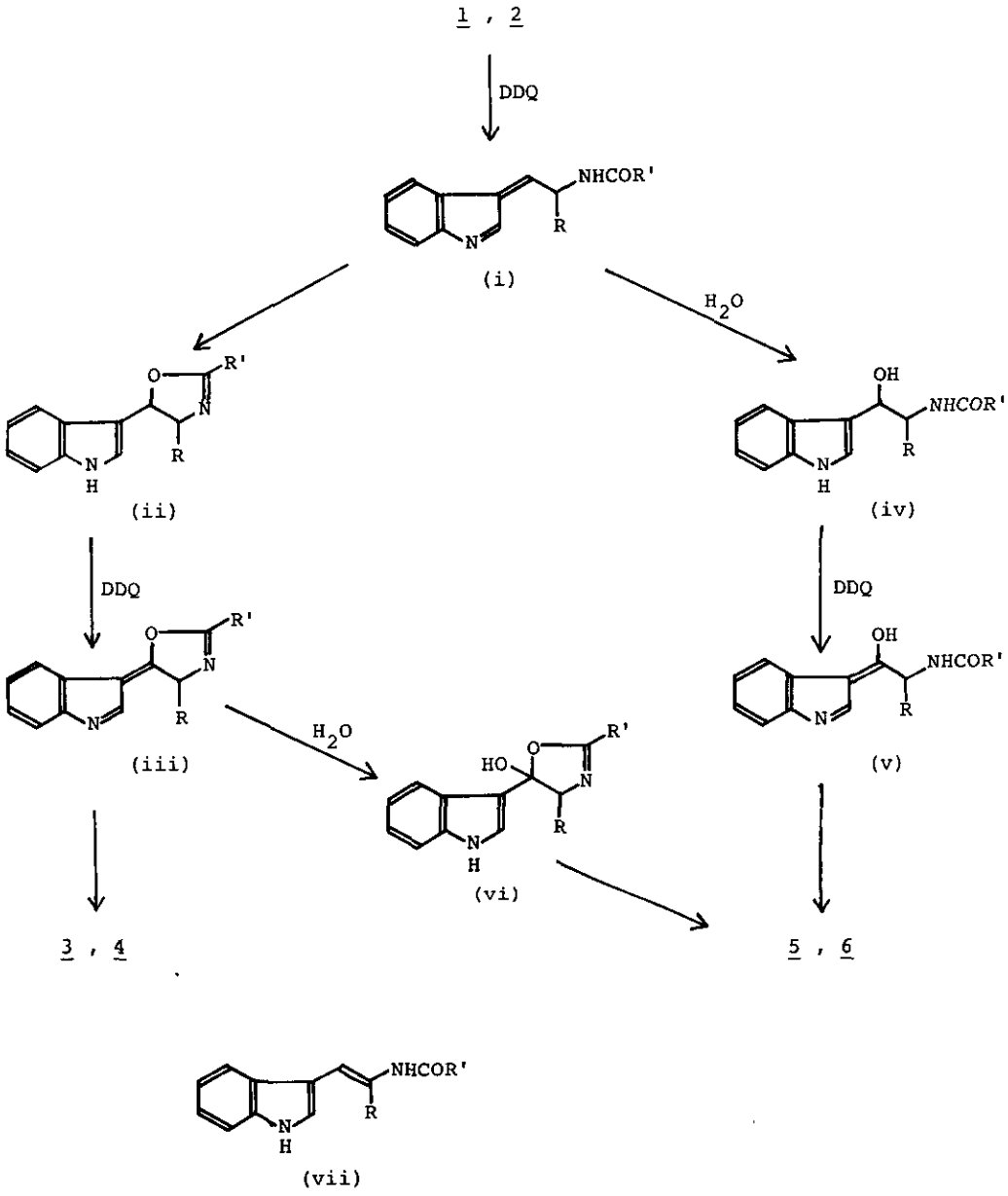
Table III. Oxazolylindoles (3) from 5 by Dehydrative Cyclization with $POCl_3$.

	R'	Yield(%)	mp°C
b	CH_3	82	202-203
c	CH_2CH_3	86	161-163
d	$CH(CH_3)_2$	85	135-136
e	C_6H_5	80	225-226
f	p-$CH_3OC_6H_4$	83	205-206
h	$CH_2C_6H_5$	92	198-200

Although the exact mechanism of this oxidation is still not clear because of no detailed mechanistic studies, the data in Tables I and II leads us to assume that the principal processes can be described as shown in the following scheme. Under the anhydrous conditions, four consecutive reactions, dehydrogenation, intramolecular nucleophilic addition, another dehydrogenation, and isomerization presumably occur to give the oxazolylindole derivatives (3, 4). The second step (i→ii) must be affected by R', i.e., accelerated by electron-donative substituents, whereas retarded by electron-withdrawing ones. Acctually, the oxidation of 2e and 2f was completed within 10 min, whereas a few hours were required in the cases of 2b, 2d, and 2g. The route via vii is improbable because no traces of vii were detected in all cases even in the oxidation with equimolar DDQ. The difference in yield between 3 and 4 owing to R can be explained in terms of the reactivity difference in the final step (iii→3, 4).

Under the aqueous conditions, all the starting materials (1, 2), except 2e and 2f, gave readily the corresponding β-keto derivatives (5, 6). In these cases, the second step must have changed from the intramolecular nucleophilic addition to the intermolecular addition of H_2O (i→iv), followed by another dehydrogenation and isomerization. However, in the oxidation of 2e and 2f, again the cyclization (i→ii) rather than the addition of H_2O must have occurred even in aqueous solvents because of electron-donative substituents (R') and then formed 4e and 4f via iii just as in the anhydrous solvents. If this is the case, 1e and 1f having the same electron-donative groups must also give the intermediates iii, followed by the addition of H_2O to give another intermediates vi, which readily changed to the β-keto compounds (5e, 5f), probably because the isomerization (iii→3) without assistance of carbomethoxy groups must be difficult to occur.[12]

Improvements of the direct synthesis of oxazolylindoles by the DDQ oxidation are now in progress.



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8. The biosynthesis of pimprinine is presumably initiated by the side chain oxidation of tryptamine and/or tryptophan derivatives, though no reports have been published.
9. For the removal of 2,3-dichloro-5,6-dicyanohydroquinone (DDHQ) the following method is more practically useful than the alumina column method: After evaporation of the THF, the residues were treated with 0.1 N NaOH and the precipitated solids were collected by filtration, washed with H_2O and a small amount of EtOAc to decolorize, and then dried to give the products in almost pure states. DDHQ recovered from the alkaline solutions can be readily reverted to rather expensive DDQ.[10]
10. D. Walker and T. D. Waugh, J. Org. Chem., 30, 3240 (1965).
11. Oxiation of 2f in more aqueous THF (THF:H_2O = 3:1) under dropwise addition of DDQ gave the β-keto product (6f) in 34% yield as well as 4f (20%). This result shows that the formation of 4f and 6f is competitive depending on the concentration of H_2O.
12. The formation of 4e and 4f via the corresponding β-keto products, 6e and 6f, (6→vi→4) is very improbable, because the isolated 6f was completely stable at room temperature even in the presence of TsOH.

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